

Vitamin A and Urolithiasis

A Review

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HIGGINS^{4, 5} is the chief proponent of the view that insufficient intake of vitamin A has a specific effect in the production of urinary calculi and that the stones may be dissolved by acid ash diet and increased intake of vitamin A. His opinion is based upon the experimental production of calculi in rats fed on diets deficient in vitamin A. In 1917, Osborne, Mendel and Ferry¹³ reported stones in the bladder in 81 of 857 rats at necropsy, and it was noted that all rats with calculi had been fed on diets deficient in fat-soluble vitamins. Higgins,⁵ in reporting later on the experimental production of calculi in rats by the feeding of diets deficient in vitamin A observed that the calculi were associated with three changes in the urinary tract: (1) keratinization of the urinary epithelium, (2) urinary infection, and (3) alkaline urine. The addition of vitamin A to the diet caused the urine to become acid and the calculi previously formed dissolved.

This subject was reviewed by the Council on Pharmacy and Chemistry of the American Medical Association in 1935.¹⁶ The Council concluded that there is no doubt that urinary stones may be produced in experimental animals by diets deficient in vitamins A and D, and unbalanced in mineral content. But the majority of investigators failed to find that a deficiency of vitamin A alone will cause stones. Keyser⁹ pointed out in 1935 that the experimental work of Higgins was done on rats, a species phylogenetically rather remote from man. He also noted that the occurrence of lithiasis was a late stage in progressive malnutrition, other prominent and concomitant features being biliary calculi, cachexia and changes in the cornea, in the retina and in the respiratory and alimentary tracts. These features are not ordinarily concomitants of calculous disease in man in the United States. It might also be noted that Higgins' observations suggest that the stones in the experimental animals were owing to alkaline urine, a secondary rather than a primary effect of vitamin A deficiency. This is indicated by the fact that the addition of ammonium chloride to the diet reduced the incidence of calculi, and by the fact that the urine became acid upon the administration of vitamin A.

• The early observations of Osborne, Mendel, and Ferry, and later of Higgins, showed that the incidence of urolithiasis was high in rats fed on diets deficient in fat soluble vitamins. Subsequently, the results of dark adaptation studies were interpreted as showing a relationship between vitamin A deficiency and calculous disease. However, a review of the literature including more recent data discloses that there is no evidence either clinical or experimental to support the claim that vitamin A deficiency is an etiologic factor in calculous disease in man in the United States.

Clinical reports of treatment with vitamin A have not supported Higgins' theory. For example, in 1937 Oppenheimer and Pollack¹² reported on a series of 52 patients with urinary calculi who were treated with diets rich in vitamins A, B, D, E, and G and having an acid ash with sufficient ammonium chloride added to assure a pH in the urine below 5.2. In two of these patients, the regimen seemed to precipitate uremia and acidosis. In none of the subjects was even partial solution of the calculi demonstrable by x-ray examination; in five, the size of the stone increased, and in one a new stone formed during the treatment.

The ability of the eyes to adapt to dim illumination has been used as a diagnostic test for vitamin A deficiency. Studies of dark adaptation in children have been carried out by Jeans and his colleagues, who used at first the Birch-Hirschfeld photometer. Jeans and Zentmire⁷ examined 404 rural and village school children of Iowa from 6 to 15 years of age and found extensive night blindness in 26 per cent of the rural and 53 per cent of the village children. The early studies of Jeans and others were interpreted as showing that vitamin A deficiency was rather prevalent in the United States, and this interpretation has been cited in support of the postulation that avitaminosis A is an etiological factor in the production of urinary calculi. Subsequent investigations, however, have not supported the conclusions of Jeans and his colleagues. For example, Palmer and Blumberg¹⁴ and Isaacs, Jung, and Ivy⁶ failed to confirm the re-

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sults with Jeans' methods and seriously questioned their reliability. Steven and Wald,¹⁵ in reviewing this subject, said that the methods of dark adaptation as originally employed apparently suffered from an uncritical appraisal of the variability of the measurements, and of the limitations of a "normal range." They said also that other methods, such as the determination of vitamin A lability or of content of vitamin A in the blood, possess a higher degree of specificity. Studies with these methods have so far indicated a relatively low incidence of vitamin A deficiency. Lindqvist¹¹ found abnormally high visual thresholds accompanied by abnormally low serum vitamin A concentrations in less than 5 per cent of a group of hospital patients particularly suspected of vitamin A deficiency. Lewis and Haig¹⁰ found only one abnormally high and vitamin A-labile threshold among 144 children, mostly from poor homes, under hospital care in New York. The lowering of the visual threshold of the dark-adapted eye by means of supplemental vitamin A was used by Steven and Wald¹⁵ as an index of vitamin A deficiency. Employing this method, a field study was conducted in Newfoundland and Labrador, an area noted for its long history of deficiency diseases. They found an incidence of vitamin A-labile thresholds of about 10 per cent, more than half of which were within the "normal range." It was their opinion that more extensive use of controlled and accurate procedures would show that even very mild deficiency in vitamin A is rare in occidental populations. Ezickson and Feldman³ studied 25 patients with calculous disease and 50 normal subjects for vitamin A deficiency by means of a dark adaptation test. They found that 24 out of 25 patients with urolithiasis showed pathologic deficiency in dark adaptation. This observation has been interpreted as supporting the vitamin A deficiency theory in spite of the fact that 14 out of 15 of their patients who were treated with vitamin A had no improvement in dark adaptation after therapy. Their work is open to the same criticism as other early studies of visual dark adaptation.

The determination of the concentration of vitamin A in the plasma is now a relatively accurate procedure. Aron,¹ in a review of the clinical significance of plasma content of vitamin A, said that under normal conditions the human organism has a tendency to maintain its plasma vitamin A at a constant level which is characteristic for the individual person; further, that daily supplements of vitamin A have no lasting effect on the vitamin A content of the blood. Aron observed that even though a rise in the amount of vitamin A in the plasma might be observed after a very large intake of the substance, the effect is transient and within ten days the plasma content is back where it was before the large intake.

On the other hand, when the oral intake of vitamin A and carotene in the diet is greatly reduced or practically nil, the amount of vitamin A in the plasma may remain unchanged for several months. The human organism has at its disposal, Aron noted, large reserves of vitamin A, 85 to 95 per cent of which are stored in the liver and the remainder in bone marrow, kidney and other tissue. He said that exhaustion of the vitamin A reserves of the body will hardly ever be observed in this country, and that when definite changes in the vitamin A content of the blood do occur in persons in the United States, they are practically always caused by some disturbance of the metabolic regulation of the vitamin, by insufficient release of the vitamin from the liver to the blood.

Jewett, Sloan and Strong⁸ compared patients having urolithiasis with normal subjects by means of dark adaptation tests and determinations of vitamin A content of the plasma. Dark adaptation tests were performed on 20 patients with urolithiasis and 40 normal controls. They were able to detect no significant difference in the two groups. Determinations of the concentration of vitamin A in blood plasma were done on 20 patients with urolithiasis and 33 normal controls. No differences in these two groups were found by this study. Autopsies were performed on 78 patients with calculi, and in none of them was there keratinization of the trachea and bronchi which, according to Blackfan and Wolbach,² are the sites of the commonest and earliest appearance of keratinization in infants that die of vitamin A deficiency.

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Cancer Diagnostic Tests

PENN REACTION

A Statement by the Cancer Commission of the California Medical Association (May 1954)

FROM TIME TO TIME, announcements appear in the press concerning new alleged cancer tests. Up to the time of preparation of this statement, not one of the numerous "blood tests" for cancer has withstood scientific investigation. Many have given rise to false positive results with distressing consequences to patients and their families.

During the last few months, there has been considerable publicity concerning a so-called seroflocculation reaction for cancer, otherwise known as a Penn or Penn-Dowdy blood test. As far as the Cancer Commission of the California Medical Association can ascertain, the following is the present status of this procedure.

1. The Penn seroflocculation reaction is not a cancer test. It is positive in a majority of patients with cancer *and* in patients who:

- (a) recently have had injury or operation;
- (b) have active rheumatoid arthritis;
- (c) have cirrhosis of the liver;
- (d) have fever over 100 degrees;
- (e) have active tuberculosis;
- (f) are pregnant;
- (g) are taking medication such as desiccated thyroid, estrogens, insulin, epinephrine and corticotropin (ACTH).

In other words, this experimental test is positive in many conditions besides cancer, and is therefore nonspecific.

2. In a certain number of patients who actually have cancer, the reaction is negative. The precise number of such false negative reactions, and of the previously mentioned false positive reactions is under investigation at present. It will take many months, if not years, to complete this investigation. The minute that reliable information concerning the value of this reaction in independent hands is available, it will be made public.

3. Should this reaction prove to be of such value as to endorse its general use, it would constitute a supplementary item of evidence in the differential diagnosis of cancer. Its proponents do not suggest, as yet, that it deserves any consideration in mass screening of asymptomatic individuals.

4. The National Research Council maintains a Committee on Cancer Diagnosis and Therapy. This committee has prepared criteria for the evaluation of diagnostic procedures. The Cancer Commission of the California Medical Association has recommended that investigators note these carefully prepared criteria and that due attention be given to them in making clinical tests on any type of proposed cancer diagnostic procedures.

5. Pending the discovery of a particular blood or chemical test, citizens are urged to utilize tried and tested methods of cancer detection. The most reliable method consists in physical examination by a qualified physician.